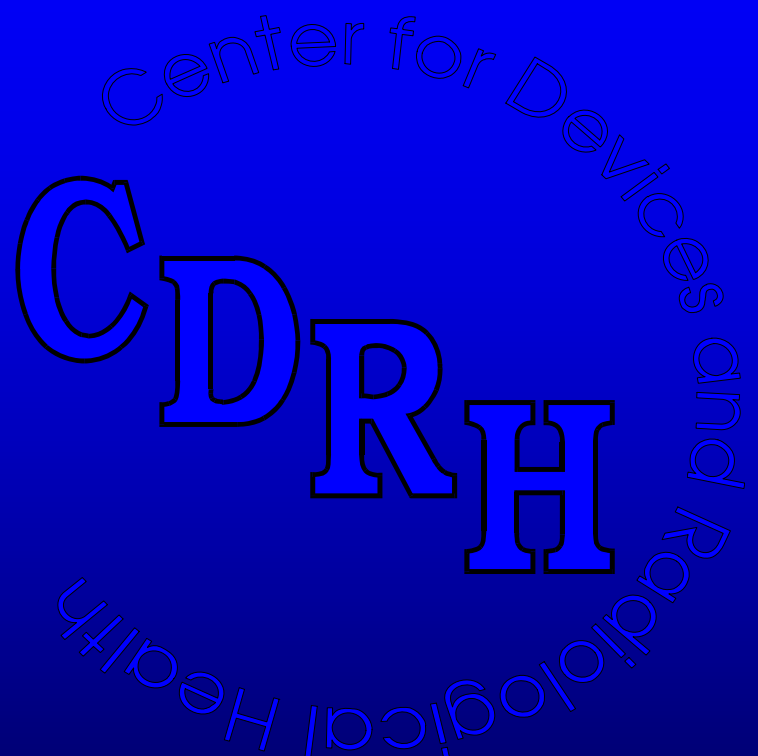
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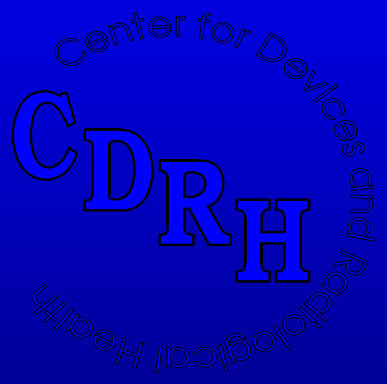
Breast Transilluminators



Radiological Devices Advisory Panel Meeting

April 12, 2012

Nancy G. Wersto, M.S. DABR
FDA/CDRH/OIVD/DRAD

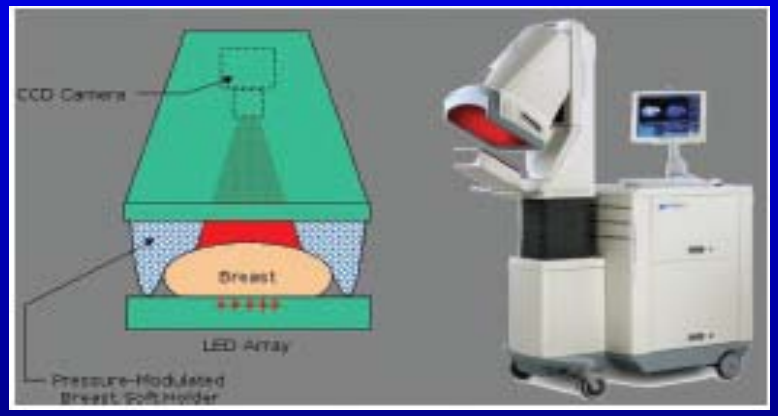
Overview of Breast Transilluminators (BrTrs)

- Background
- Regulatory History
- Literature Review
- Clinical Perspective
- Current Regulatory Status
- Panel Discussion

Background

- Lightscanners, diaphanoscopes, or optical breast imagers
- Electrically powered
- Emit low intensity visible light and near-infrared radiation (700-1050 nm)
- Device pressed against the breast to illuminate mammary tissue in a darkened environment
- Light preferentially absorbed by hemoglobin in the blood

Background (cont)



Regulatory History

- Pre-amendment device
- Commercial distribution prior to May 28, 1976
- ObGyn Devices Panel Meeting on January 11, 1991
- FDA issued a final rule in 1995 classifying them as Class III
- We are here today to discuss the Citizens Petition for reclassification and to complete the classification process

Regulatory History (cont)

Medical Device Classification

- Class I — General controls sufficient for reasonable assurance of safety and effectiveness (S&E), e.g., stethoscopes
- Class II — General controls alone are insufficient for a reasonable assurance of S&E but there is adequate information for Special Controls, e.g., most imaging and therapy devices such as CT, MRI, FFDM, US and linear accelerators
- Class III — General controls insufficient for reasonable assurance of S&E and there is inadequate information for Special Controls for S&E, e.g., breast tomosynthesis

Regulatory History (cont)

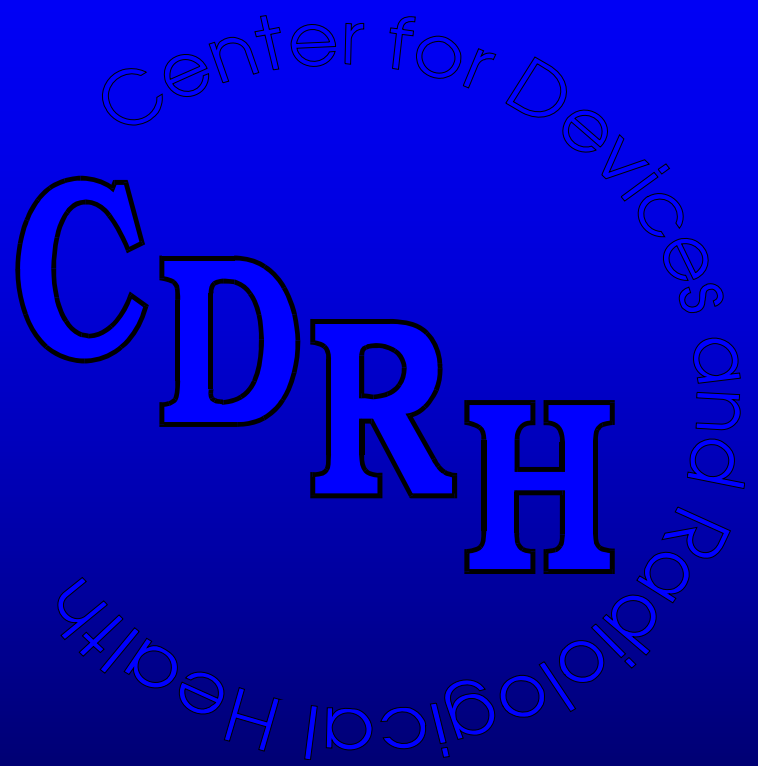
21 CFR § 892.1990 Transilluminator for breast evaluation.

(a) Identification. A transilluminator, also known as a diaphanoscope or lightscanner, is an electrically powered device that uses low intensity emissions of visible light and near-infrared radiation (approximately 700–1050 nanometers (nm)), transmitted through the breast, to visualize translucent tissue for the diagnosis of cancer, other conditions, diseases, or abnormalities.

(b) Classification. Class III (premarket approval).

(c) Date premarket approval (PMA) or notice of completion of a product development protocol (PDP) is required. The effective date of the requirement for premarket approval has not been established.

See § 892.3. [60 FR 36639, July 18, 1995]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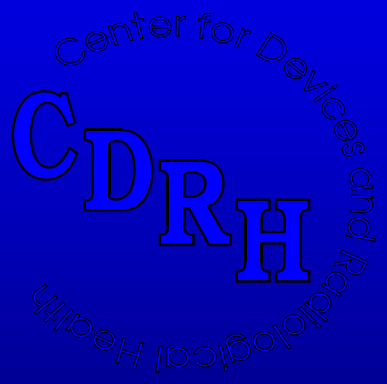
Systematic Literature Review of Breast Transilluminators



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Epidemiologist
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Office of Surveillance and Biometrics

Outline

- Objectives
- Methods
- Findings on safety and effectiveness of Breast Transilluminators
    I. Overview of the Published Literature
    II. Effectiveness
    III. Safety
- Discussion of strengths and limitations
- Conclusion

Objectives

- What is the evidence for effectiveness of breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities?
- What are the reported adverse events associated with the use of breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities?

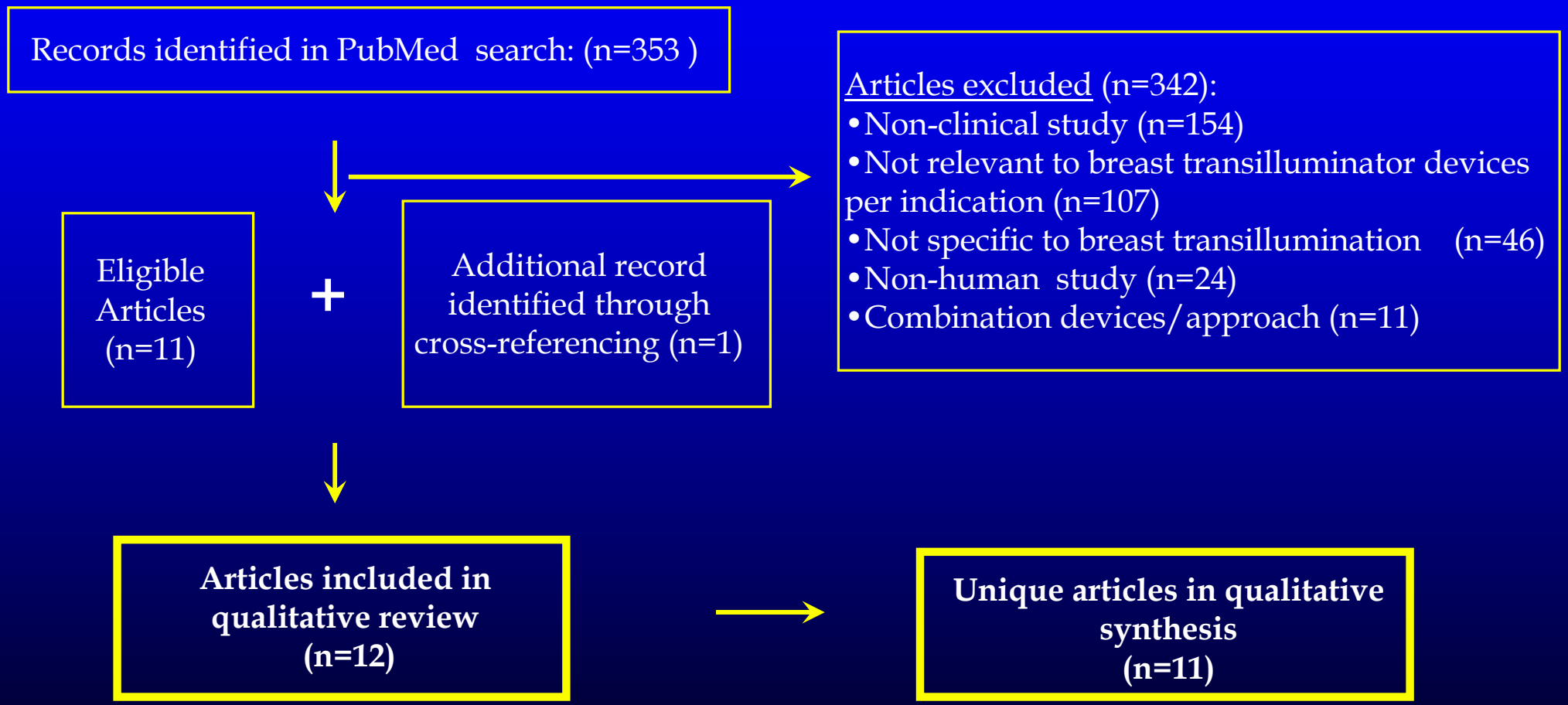
Methods

- Searched PubMed database using the following terms:
  - "lightscanner or transilluminator or diaphanoscope"
  - "near-infrared"
  - "optical"
  - "breast or mammary or carcinoma or cancer or tumor or malignant"
- Timeframe: January 1, 1991 – February 23, 2012
- Language limited to English publications

Inclusion Criteria

- Devices that uses 700-1050nm on the breast for the diagnosis of cancer, other conditions, diseases or abnormalities
- Randomized Controlled Trials (RCT)
- Observational studies
- Systematic literature reviews
- Meta-analyses

Article Retrieval and Selection



Systematic Literature Review: Study Characteristics

- Eleven articles
  - Cross-sectional study (n=9)
  - Retrospective study (n=2)
- Study populations: US and European
- Sample size: 18 - 610 subjects
- Imaging modalities: hand-held transilluminator, optical mammography, optical tomography

Systematic Literature Review Question 1

What is the evidence for effectiveness of breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities?

Effectiveness: Factors that can affect interpretability

- Comparator
- Performance Measures
  - Standalone (N=6) *vs.* Adjunctive use (N=5)
- Reader Variability
- Factors that may affect effectiveness: age, race, menopausal status, breast density, lesion size & depth

Effectiveness: Comparator

- Histology (n=8)
- X-ray mammography (n=2)
- Magnetic resonance imaging (n=1)

Effectiveness: Performance Measures

- Sensitivity (N=7), specificity (n=5), positive predictive value (N=3), negative predictive value (N=3), percent agreement (N=1), receiver operator curves analyses (N=3)
- Performance measures by study populations
  - Majority evaluated sensitivity for breast carcinoma
  - One evaluated specificity for women without breast cancer
- Scale of reporting: dichotomous

Effectiveness: Standalone use

- Performance Measures
  - Sensitivity, Specificity, PVP, NPV

Study	Sample size	Sensitivity	Specificity
Jarlman 1992a	36 breast cancer, 473 normal	86% (0.70, 0.95)* NPV: 99%	82% (0.79, 0.85)* PPV: 23%
Jarlman 1992b	243 breast cancer	72% (0.65, 0.77)*	N/A

  - Screening population: (Braddick 1991) Sensitivity: 7.7% (0.8, 43). Specificity 97.6 (97.2, 98)

* All 95% CIs were calculated from reported sensitivity and sample size from using exact methods

Effectiveness: Standalone use (cont.)

- Performance Measures
  - Percent agreement

Study	Sample size	Positive per cent agreement	Negative per cent agreement
Jarlman 1992a	36 breast cancer, 473 normal	X-ray mammography 78% (0.61, 0.90)*	X-ray mammography 80% (0.76, 0.83)*

* All 95% CIs were calculated from reported percent agreement and sample size from using exact methods

Effectiveness: Standalone use (cont.)

- Performance Measures
  - Area under the curve (AUC)
    - Poplack 2007 : AUC= 0.67 (95% CI: 0.52, 0.82)
    - Schneider 2011: From ROC amplitude cut-off: Sensitivity 85.7%, Specificity: 87.5%, PPV: 92.3%, NPV:77.8%

Effectiveness: Adjunctive use

- Adjunctive Use: lesions identified using x-ray mammography prior to optical imaging
- Performance Measures: Sensitivity, Specificity, PPV, NVP

Study	Sample size	Sensitivity	Specificity
Cheng 2003	48 patients	92% (0.61, 0.99)* NPV: 96%	67% (0.49, 0.81)* PPV: 48%
Athanasiou 2007	71 patients with BIRADS 4/5	73% (0.57, 0.86)	39%(0.25, 0.53)
Poellinger 2011	21 breast lesions BIRADS 4/5	92% (88.6, 95.4)*	75%(68.1, 81.8)*
Grosenick 2005 Rinneberg 2005	102 breast cancer	90% (0.82, 0.94)*	N/A

- Performance Measures: Area Under the Curve (AUC)
  - Poellinger 2008: Mean AUC difference: 0.07

* All 95% CIs were calculated from reported sensitivity and sample size from using exact methods

Effectiveness:
Reader Variability

- One study estimated intra- and inter-observer agreement
  - Poellinger 2011
    - κ=0.48, precontrast
    - κ=0.41, late fluorescent
    - κ=0.43, agreement with x-ray mammography

Effectiveness: Discussion

- Performance by lesion characteristics
  - Lesion size (N=6)
    - Malignant lesions: 8mm – 80mm
    - Benign lesions: 10mm – 52mm
  - No formal statistical analyses
  - Lesion depth: None
- Performance by other factors
  - No formal analyses by age, BMI, race, menopausal status, breast density

Systematic Literature Review Question 2

What are the reported adverse events associated with the use of breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities?

Safety

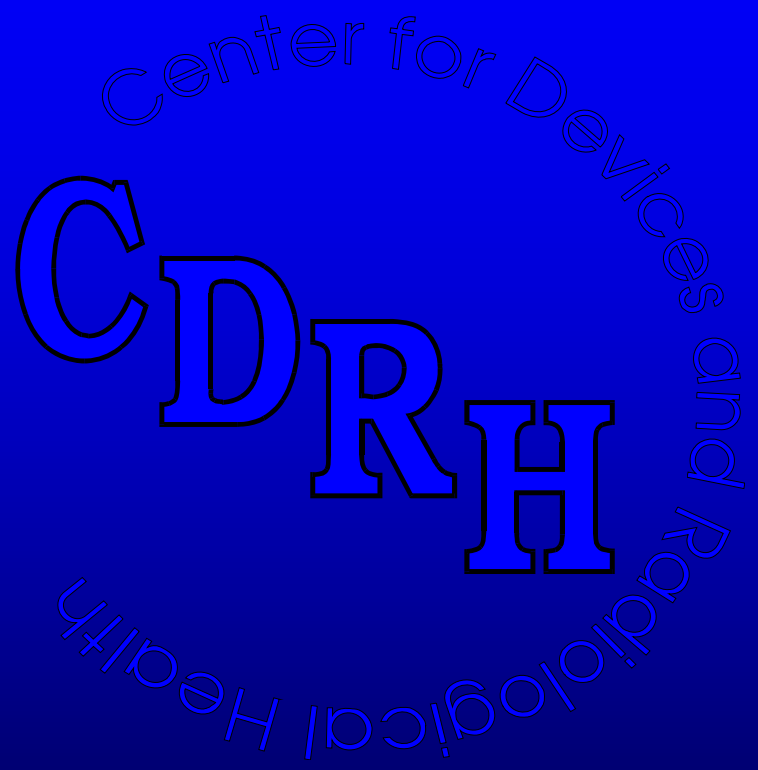
- None of the studies reported whether or not any adverse events had occurred

Strength and Limitations

- Histopathology was the choice of comparator (N=8)
- No randomized controlled trials or prospective studies
- Limited test performance information for women without cancer or benign cancer
- Limited information on the variability of readers

Summary:
Effectiveness and Safety

- Effectiveness of breast transilluminators is not adequately demonstrated
- Safety related to test performance of breast transilluminators could not be assessed
- Additional studies to address the effectiveness and safety of breast transilluminators are needed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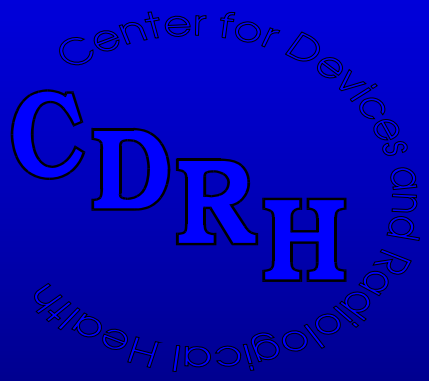
Breast Light Scanning Clinical Perspective



Helen J. Barr, MD
Division Director
Division of Mammography Quality and Radiation Programs
Office of Communication, Education, and Radiation

Outline

- Concept behind breast light scanning
- Limitations of the technology
- Summary of early breast light scanning research
- Current clinical breast work-up
- What a breast diagnostic device needs to be

Concept

- Light in red and near infrared range is absorbed by hemoglobin
- Absorption of light would be different in benign and malignant tissue and therefore they could be distinguished from each other

Limitations

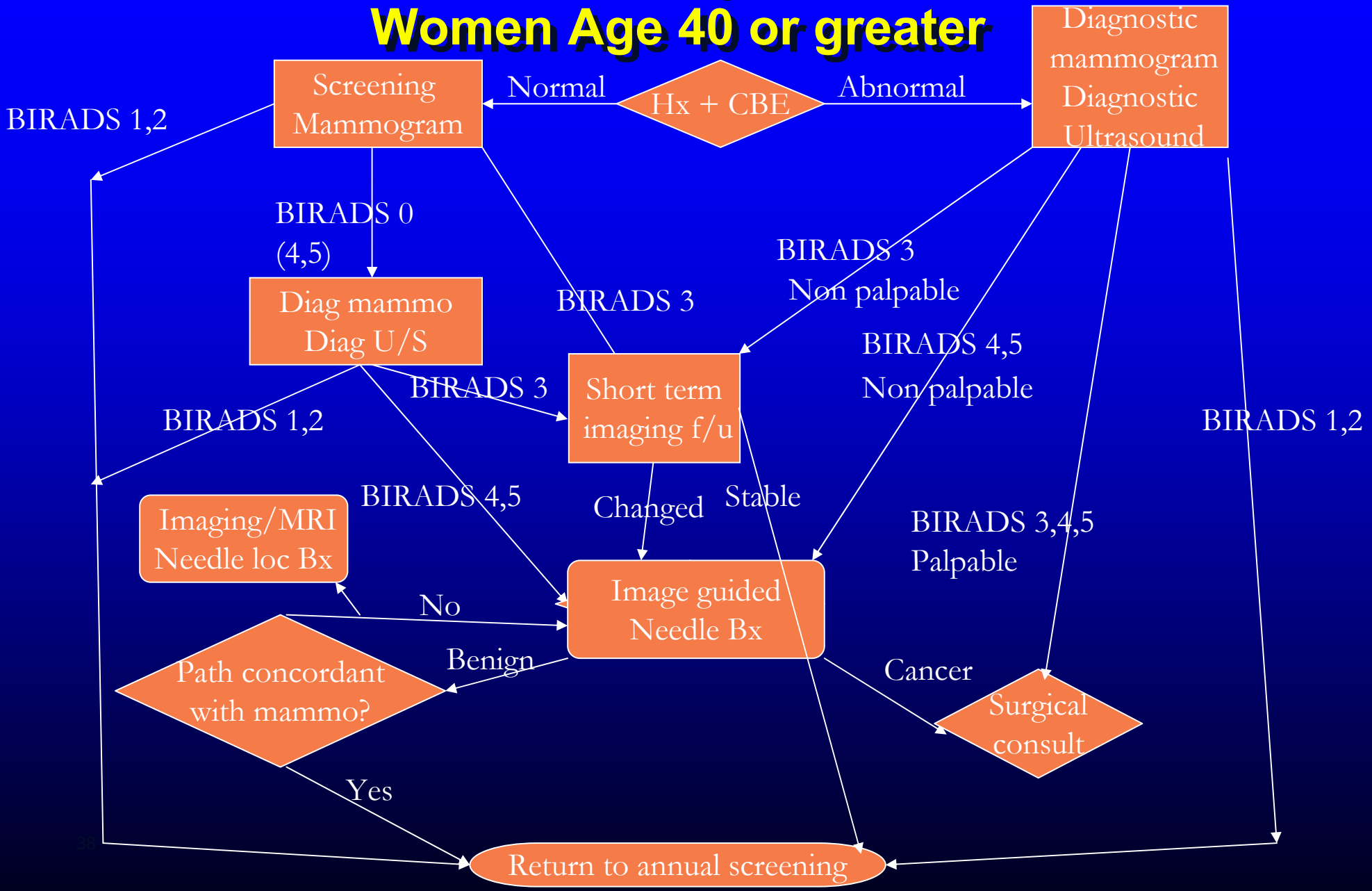
- Hemoglobin absorbs light whether in a lesion, a vessel, or free in tissue – false positives
- Indirect signs such as increased vascularity and abrupt vessel caliber change, especially without flow parameters, are not reliable indicators of malignancy
- Penumbra effect – need all portions of breast close to the skin to ameliorate structural shadows obscuring smaller lesions

Conclusions of D'Orsi NIH-funded study of Breast Light Scanning*

- Sensitivity not high enough to detect lesions under 1 cm in size – should not be used for screening
- Specificity too low – should not be used alone for diagnosis because it doesn't reliably distinguish between benign and malignant lesions
- No known adjunctive use

*D'Orsi CJ, Smith EH: Double blind study of breast diaphanography. National Institutes of Health Grant G2736 1984-1989 RNM#1R01CA37970-AIA

Breast Work-Up in the US: Women Age 40 or greater



Characteristics of a Useful Diagnostic Breast Imaging Device

- High Specificity – distinguish benign from malignant
- Reasonable Sensitivity – needs to detect lesions less then 1 cm
- Usable across range of patient populations (e.g. dense breasts, large breasts) or populations limitations spelled out
- Low operator variability - high reproducibility
- Detects signs that reliably indicate presence or absence of disease

Characteristics of Breast Light Scanners

- Low sensitivity – for lesions under 1 cm in size
- Low specificity
- High operator variability - low reproducibility
- Interpretation based on unreliable signs

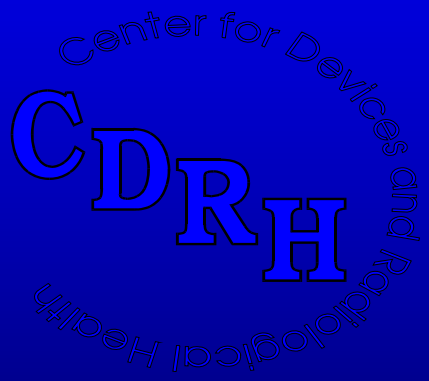
Major Risks of Breast Light Scanning Identified by 1991 Panel : Still True?

- **Misdiagnosis** - failure of device to differentiate between benign and malignant lesions may lead to incorrect patient management decisions
- **Delayed Diagnosis** - false negative results may lead to delays in the timely diagnosis of breast cancer
- **Delayed Treatment** - allows an undetected condition to worsen and potentially increases morbidity and mortality

Petitioner's Presentation on additional clinical information

- First Source (UK 2007/2008 -1087 users)
  - Market Research Survey
  - Not found in peer reviewed literature
  - Data on product use
- Second Source (UK 2009 – 300 patients)
  - Not found in peer reviewed literature
  - Observational study in symptomatic women
- Third Source (UK 2009/2010-53 patients)
  - Not found in peer reviewed literature
  - Data from a questionnaire; validity of instrument unknown

Breast Transilluminators Current Regulatory Status



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Division of Radiological Devices
OIVD/CDRH

Current Regulatory Status

- Proposed rule on January 13, 1995
- Final rule on July 18, 1995 for BrTrs placed in Class III under 21 CFR 892.1990
- Premarket Application (PMA) or PDP required
- 515(b) of FD&C Act requires the FDA to “call for PMAs” by specifying a date in the FR
- Process requires notice-and-comment rulemaking

Current Regulatory Status (cont)

- In response to a requirement in the Act (515(i)) to set a schedule to "call for PMAs" for all remaining pre-amendment class III devices:
  - Proposed rule on August 25, 2010
  - BrTrs placed in Class III
  - Intent to establish effective date requiring PMA or PDP
  - Opportunity for public comment

Current Regulatory Status (cont)

- Citizen petition received on September 9, 2010
- BrTrs were reported by petitioner as Class I devices outside U.S.
  - differences in regulatory requirements between CE Mark & FDA clearance
- Petitioner states the device risks are adequately mitigated

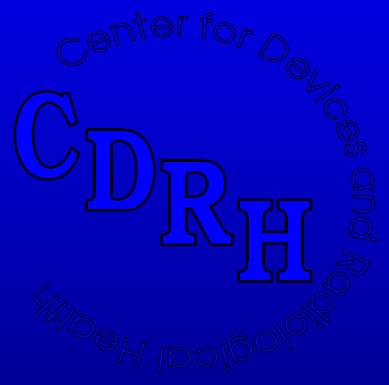
Current Regulatory Status (cont)

- Petitioner states the device is designed to be a "non diagnostic product"
- Petitioner evidence of safety and effectiveness:
  - 3 sources of additional clinical information
- Requests Class I for BrTrs for a non-diagnostic device

Panel Discussion

- Review risks and identify new risks
- Consider appropriate risk mitigations
- Evaluate the merits of the Citizen Petition
- Determine whether valid scientific evidence demonstrates reasonable assurance of safety and effectiveness of BrTrs
- Come to consensus on appropriate classification based on the evidence

Breast Transilluminator Panel Discussion



Radiological Devices Advisory Panel Meeting

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Assurance of Safety

21 CFR §860.7(d)(1)

"There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks."

Assurance of Effectiveness

21 CFR §860.7(e)(1)

"There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a **significant portion of the target population**, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, **will provide clinically significant results**."

Valid Scientific Evidence

21 CFR §860.7(c)(2)

"Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness."

Medical Device Classification

- Class I : General Controls alone
- Class II : General Controls and Special Controls
- Class III :
  - General controls insufficient
  - Inadequate information for Special Controls

General Controls – Class I

- Establishment Registration
- Medical Device Listing
- Manufacturing using Good Manufacturing Practices (GMPs)
- Appropriate Labeling
- Submission of a 510(k) premarket notification prior to marketing

Special Controls – Class II

- Submission of a 510(k) premarket notification prior to marketing
- Special labeling requirements
- Mandatory performance standards
- Guidance Documents
- Consensus Standards
- Postmarket Surveillance

Class III Medical Devices

- Devices where a reasonable assurance of safety and effectiveness has not been demonstrated
- Devices for which both General and Special Controls are not sufficient to provide a reasonable assurance of safety and effectiveness

Panel Discussion: Question 1

- The key risks to health of breast transilluminators identified by the Obstetrics and Gynecology Devices Panel include:
  - missed diagnosis
  - delayed diagnosis
  - delayed treatment
  - electrical shock
  - optical radiation
- Identify any additional risks to health that should be addressed with respect to breast transilluminators for the diagnosis of cancer, other conditions, diseases, or abnormalities

Panel Discussion: Question 2

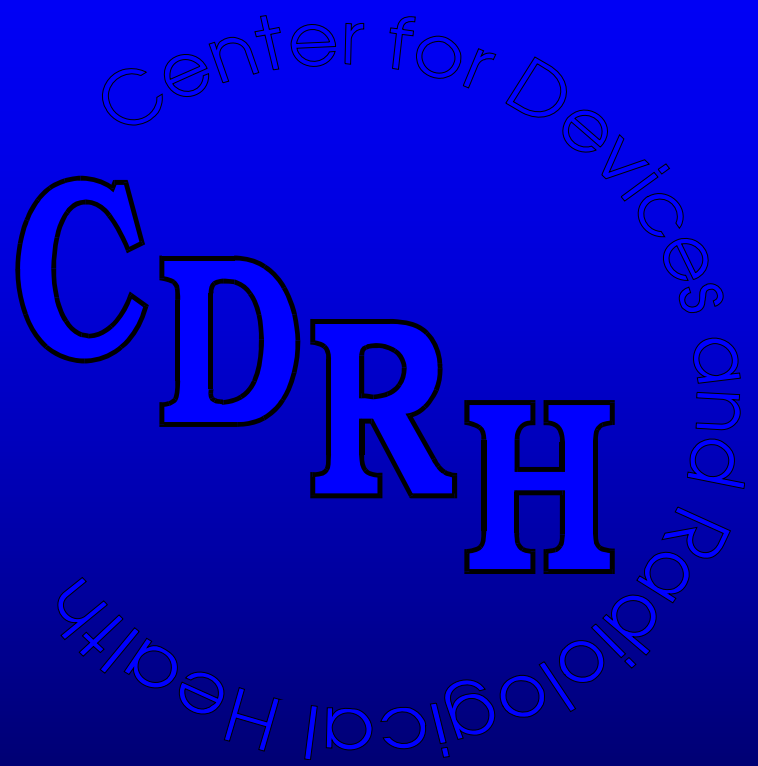
- Class I medical devices are those for which General Controls are sufficient to provide a reasonable assurance of safety and effectiveness
- Discuss whether you believe General Controls alone adequately mitigate the risks associated with breast transilluminators for the diagnosis of cancer, other conditions, diseases, or abnormalities

Panel Discussion: Question 3

- Class II medical devices are those for which Special Controls in addition to General Controls are necessary to provide a reasonable assurance of safety and effectiveness
- Is there sufficient information to establish Special Controls for breast transilluminators?

Panel Discussion: Question 3 (cont)

- Would the addition of Special Controls to General Controls mitigate the risks?
- What should the Special Controls include?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Backup Slide$_1$

The abstract of a trial that took place at City Hospitals Sunderland was presented at the European Institute of Oncology's 12th Breast Cancer Conference in Milan on 17th June 2010

Breastlight is a handheld device which utilizes a light source of 617 nm

300 patients recruited and 58 biopsies performed

18 women with cancer diagnoses and 40 benign tumor diagnoses

Sensitivity: 67% (12 detected/18 malignant lesions)

Tumor size varied 0.7-3.8 cm

Specificity: ?

Sensitivity for benign lesions: 17.5% (7 detected/40 benign lesions)

False positive rate: 3.2% (7/220 non-malignant cases)

Backup Slide$_2$

- **Regulatory oversight for Class I devices in Europe and Canada:**
  - **For EU Medical Device Directive Class I devices are subject to self-regulation**
  - **For Health Canada Class I devices do not require a Medical Device license**